UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,614	01/09/2002	Ya Fang Liu	YFLU-P03-001	6176

23628 7590 11/16/2006

WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,614	LIU, YA FANG	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34 and 44-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance.. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/1/06 has been entered.

The response and amendment filed 8/1/06 are acknowledged.

Claims 33, 34 and 44-47 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 33, 34, 44 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (US 6,943,000; "Davis") in view of Reynolds et al. (1997; "Reynolds").

Davis discloses *in vitro* and *in vivo* methods for screening inhibitors of JNK3 for diseases involving excitotoxicity such as Alzheimer's disease, Huntington Disease, Parkinson's disease and ischemia (abstract). Candidate compounds can be tested in cell or tissue culture as well as animal models. Davis teaches, for example, that cells expressing JNK3 can be incubated with the test compound. Lysates can be prepared from treated and untreated cells and Western blotted. Antibodies for JNK3 can be used to assess the amount of JNK3 expression in the treated and control cells. Alternatively, test compounds can be administered to cell cultures with radiolabelled ATP. The amount of phosphorylation of a JNK3 substrate can be measured and compared to a control (col. 9, lines 55-65). The radiolabelled phosphorylation assay can also be accomplished by incubating an isolated JNK3 and a JNK substrate such as ATF2, Elk-1 (col. 26, lines 35-64) or c-Jun (col. 10, lines 29-31). This disclosure meets the limitations

of instant claim 33, parts a and b, because Davis discloses incubating a test compound with a JNK and its substrate, wherein the degree of the phosphorylation of the JNK substrate is a measure of its ability to inhibit JNK. The disclosure of the use of c-Jun and a phosphate donor meets the limitations of instant claim 47. The disclosure of JNK3 meets the limitation of instant claim 34 regarding the isoforms type of JNK.

Test compounds predicted to inhibit JNK3 activity can be administered to animals as models for the various disease paradigms. The treated animal is then assayed for inhibition of the JNK activity by observation of the anima or by directly measuring JNK3 expression in neural tissue removed from the animal and comparing the result to a control (col. 10-11, bridging paragraph). Davis also discloses that neuronal apoptosis can also be assessed by TUNEL assay to evaluate whether a JNK3 modulator is affecting apoptosis (col. 25, lines 23-26). Davis demonstrated the utility of TUNEL to assess apoptosis associated with JNK3 modulates by administering kainic acid (KA) to two sets of mice. One set of mice was positive for hippocampal neurons expressing JNK3 while the other set was deficient. After KA administration, the mice were sacrificed and the hippocampal tissue was stained with crystal violet and subjected to TUNEL assay. The tissue from mice having normal JNK3 expression exhibited apoptosis while JNK3-negative mice had normal hippocampal regions (see Example 7, columns 23-25). This disclosure meets the limitations of instant claim 33, parts c-e because Davis teaches the administration of a compound to an animal, harvesting neuronal tissue, determining apoptosis in the sample and comparing the result to a control.

Davis does not disclose that the JNK kinase is present in the in vitro assay in an amount of about 0.5 to 2.5 micrograms of purified JNK or that the JNK substrate is present in an amount of about 1 to about 3 micrograms.

Reynolds discloses an assay to measure the phosphorylation of τ, the microtubule-associated protein (MAP) in axons, and τ peptides by protein kinase A, JNK and GSK3. The assay was carried out by measuring the incorporation of 32P from [γ-32P] ATP into the substrate using varied reaction conditions

with each of the kinases. Purified rat JNK was obtained from a commercial source (p. 1737, left column, middle of "Materials" section). Figure 1 shows that the substrate τ was present in an amount from, 11-22 μg. Another substrate, GST-c-Jun (a c-Jun fusion protein) was present in an amount of 2.5 μg. JNK was present in the amounts of 0.25 μg, 0.17 μg, 0.5 μg, or 2 μg. the phosphorylation experiments clearly demonstrate the variation in substrate and kinase concentrations.

It would have been obvious to employ JNK kinase and the JNK substrate in the amounts of about 0.5 to 2.5 micrograms and about 1 to about 3 micrograms, respectively, in the assay of Davis to determine inhibitors of JNK3. The ordinary artisan would have been motivated to do so because Davis and Reynolds employ the same type of radiolabelled ATP assay to determine JNK kinase activity. The ordinary artisan would have had a reasonable expectation that the kinase an substrate ranges used by Reynolds could be used successfully by Davis because the assays used by Davis and Reynolds are comparable (use of the same buffers, additive, etc.).

Furthermore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to choose appropriate limitations on the ratio between the rates of formation of products and reactants, reaction time periods and the maximum concentration of the product in the reaction milieu. One skilled in the art would be motivated to optimize reaction conditions to obtain an increased product yield. According to *In re* Aller 105 USPQ 233,

> Normally, change in temperature, concentration, or both, is not patentable modification; however such changes may impart patentability to process if ranges claimed produce new and unexpected result which is different in kind and not merely in degree from results of prior art; such ranges are termed critical ranges, and applicant has burden of proving such criticality; even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if modification within capabilities of one skilled in art: more particularly, where general conditions of claim are disclosed in prior art, it is not inventive to discover optimum or workable ranges by routine experimentation.

Enzymatic phosphorylation of JNK kinase substrates and the optimization of variables that control radiolabelled kinase assays are well known in the art. An ordinary skilled artisan would naturally

experiment with the optimum conditions of enzyme, substrate, reaction rate, concentrations, temperature, time and pH for the exploitation of success. It is apparent that the claimed process is merely different in degree and not in kind from the reference process.

Accordingly, it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to optimize the ratio between the rates of formation of products and reactants, reaction time periods and the maximum concentration of the product in the reaction milieu, especially in the absence of an objective showing of surprising or unexpected results.

Response to Applicant's Argument

Responding to Applicant's argument that Davis teaches the phosphorylation assay as one of many possible alternatives, Davis states that "Molecules that inhibit JNK3 can be identified in a high throughput screen. A molecule that is a preferred candidate to treat excitotoxic disorders inhibits JNK3, but not other protein kinases, including related MAP kinases. Candidate molecules, once identified, can be optimized using combinatorial chemical methods or by the synthesis of related can be tested for JNK3 therapy" (col. 27, lines 8-15). Thus, Davis clearly envisions the combination of *in vitro* and *in vivo* assays to optimize candidate drugs for neurological diseases related to JNK function.

Responding to Applicants argument regarding the amounts and quantities of enzyme and substrate, *vide supra*. Regarding Applicant's assertion that Davis does not teach the use of a purified JNK3 for the in vitro assays, Applicant is directed to col. 10, lines 32-36, wherein Davis teaches the use of cell lysates or purified proteins in the presence or absence or test compounds.

Claims 33, 34, 44, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (US 6,943,000; "Davis") in view of Reynolds et al. (1997; "Reynolds"), as applied to claims 33, 34, 44 and 47, in further view of Liu (1997; cited in the Office Action mailed on 6/14/05).

Applicant argues that Davis does not anticipate the elements of the claimed invention and that Liu does not supply the missing elements and that the rejection can not stand.

Responding to the argument regarding Davis, Davis has been modified in response to the amendment filed 8/1/06, *vide supra*. Responding to Applicant's argument regarding Liu, Applicant's argument is not directed to the factual basis of the rejection and is, therefore, non-persuasive.

Claims 33, 34, 44, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (US 6,943,000; "Davis") in view of Reynolds et al. (1997; "Reynolds"), as applied to claims 33, 34, 44 and 47, in further view of Gnegy et al. (1976, "Gnegy").

Applicant argues that Davis does not anticipate the elements of the claimed invention and that Liu does not supply the missing elements and that the rejection can not stand.

Responding to the argument regarding Davis, Davis has been modified in response to the amendment filed 8/1/06, *vide supra*. Responding to Applicant's argument regarding Gnegy, Applicant's argument is not directed to the factual basis of the rejection and is, therefore, non-persuasive.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Susan Hanley
Patent Examiner
AU 1651

Leon B. Lankford, Jr.
Primary Examiner
Art Unit 1651